REMARKS

Status of the Claims

Claims 23 and 28-38 have been withdrawn from consideration by the Examiner, leaving Claims 21, 22, 24-27 and 39 under examination. Claims 21, 26, and 37 have been amended and new Claims 40-45 have been added. Claims 21-45 are now pending.

Amendments to the Specification

The specification has been amended to correct an apparent formatting error. At page 52, there is a listing of various compounds. Compound 250 (the last compound on the page) was truncated by the right margin. As such, the methoxy group on the molecule is shown only as –Ol. This error has been corrected by the present amendment. The correct structure for Compound 250 was originally filed in Claim 6, page 148, so this amendment does not add new matter to the specification.

Amendments to the Claims

Claim 21 has been amended to include "alkoxy" in the list of substituents for R10. Support for this amendment can be found in the specification at page 20, lines 5-11, where general formula I is provided and R1 is said to be a "substituted heteroaryl," which, according to the definition on page 18, lines 20-29, is a heteroaryl substituted with, *inter alia*, "alkoxy" (*see* specifically line 23). See also compound 250, which is a representative example of a compound of Formula VI having R10 as alkoxy.

Claims 26 and 37 have been amended to delete compounds 228, 229, and 230.

New Claims 40-45 have been added. Support for these new claims can be found on page 23, lines 7-27, of the application.

No new matter has been added by the amendments herein; therefore, examination is requested on the amended claims. No additional claims fees are required for the five new claims because Applicants originally paid for nineteen claims over twenty at the time of U.S. National Phase entry.

Information Disclosure Statement

The Examiner acknowledged receipt of the information disclosure statement of December 15, 2009, and indicated that all of the references cited therein were considered, except one. The Examiner indicated that Reference WO 00/78761 was lined through

because it was already cited on Form PTO-892. However, the Examiner appears to have lined through the wrong reference; Reference WO 00/33836 was lined through instead of WO 00/78761. Thus, enclosed herein in the information disclosure statement is another copy of WO 00/33836 to ensure that this reference is considered by the Examiner.

Rejection under 35 U.S.C. § 103(a)

In the Office Action, the Examiner maintained the rejection of Claims 21-22, 24-27, and 39 as allegedly being unpatentable over WO 2000/78761 to Bannister *et al.* (hereinafter Bannister). Applicants again respectfully traverse this rejection and submit that the Examiner has not set forth a *prima facie* case of obviousness.

Standard for Obviousness

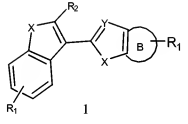
The legal standard for an obviousness determination requires factual inquiries involving: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations such as commercial success and satisfaction of a long-felt need. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently reaffirmed the evaluation of these so-called "Graham factors" for a proper obviousness analysis. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). In *KSR*, the Supreme Court went on to say that "rejections on obviousness ground cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418.

When analyzing a chemical compound under *KSR*, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). *Prima facie* obviousness for a chemical compound is therefore established by identifying some reason that would have led one of ordinary skill in the art to select and then modify a known compound (*i.e.*, a lead compound) in a particular way to achieve the claimed compound. The current Office Action contains errors in evaluating these requirements: (1) the Examiner failed to identify a known lead compound and (2) the Examiner failed to provide the reasoning that would have led a chemist to modify the lead compound in a way that would have resulted in the claimed compounds.

1. Identification of the Lead Compound

The question of obviousness "often turns on the structural similarities and differences between the claimed compound and the prior art compound." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). Thus, an obviousness allegation based on structural similarity between claimed and prior art compounds "**clearly depends** on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." *Takeda*, 492 F.3d at 1359 (emphasis added); *see also Eisai Co. Ltd.* 533 F.3d at 1359 (stating that "post-KSR, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art).

In the present rejection, the Examiner did not specifically identify a known compound that one of ordinary skill in the art would have selected as a lead compound in order to then make the needed modifications to arrive at the elected compound. What the Examiner did instead was to rely on a broad genus of compounds from Bannister, which includes a vast number of unknown compounds, and then pick a hypothetical compound. In particular, the Examiner simply relied on the assertion that "Bannister teaches compounds of the following general formula:



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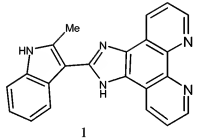
wherein X can be NR, and R can be H, Y can be N, R_2 can be Me, R_1 need not be present, and B can be a polycyclic cycloalkyl or heteroaryl, or heterocyclic rings *inter alia* (referencing page 18)." (Office Action page 4.) The Examiner further stated that pages 10-11 of the reference further defined the terms heterocyclyl or heterocyclic group to mean phenanthroline and drew Applicants' attention to claims 2 and 7-10, as well as pages 19-20, which describe a large subgenus of compounds in which the compounds of Formula (1) have "a fused aromatic or heteroaromatic ring." (Office Action page 6.)

Given these statements it is clear that the Examiner did not base the obviousness determination upon a reasoned identification of a known lead compound. Identifying a known lead compound was simply skipped over, leaving only a blank assertion that Bannister taught the compound where X is NH, Y is N, R_2 is Me and R_1 is not present, where B can be a phenanthroline, *i.e.*, elected species compound 90. The error here maybe subtle, but it is highly significant. From the large generic formula in Bannister (and not from any particular known lead compound), the Examiner herself chose specific moieties for the various variables in the formula to arrive at the elected species compound 90. The choosing of various variables was done without explanation. In other words, the Examiner's obviousness determination began with the final conclusion—the assertion that Bannister "teaches" the elected species compound 90:



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How the Examiner got to this point, which was ignored, skips a critical part of the obviousness analysis—it is the "reasoned identification of a lead compound" that is referred to in *Eisai*. Again, *Eisai Co. Ltd.* 533 F.3d at 1359 states that "post-KSR, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art. Apparently, the only reason for arriving straight at the elected compound 90 is that it is a possibility from the "finite number of possible combinations" in the general formula of Bannister and that phenanthroline is one of a "finite number of possible options" listed for the large subgenus in which B is "a fused aromatic or heteroaromatic ring."[1] Tellingly, that is the

[1] While the definition of "heterocyclyl" or "heterocylic group" at page 11-12 of Bannister does include – amongst more than 55 other specifically named examples – phenanthroline, this definition encompasses a much larger number of "options" than just these representative examples (*i.e.* any and all 3- to 10-membered ring structures, whose structures include anywhere from 1 to 4 heteroatoms, and which may or may not be part of a polycycle). Moreover, the definition of "aryl" (*i.e.* aromatic) at page 10 of Bannister, which includes heteroaromatic, provides even more "options" for the "fused aromatic or (continued...)

same reason to conclude that every compound contemplated within the general formula of Bannister is obvious.

It follows then that one error in the Office Action is that the obviousness rejection begins without any rationale from a hypothetical compound, one where X is NH, Y is N, R_2 is Me, R_1 is not present, and B is phenanthroline. Why pick this particular hypothetical combination of substituents cited by the Examiner? That is a critical question; a "reasoned identification of a lead compound" is required. Even taking into consideration the Examiner's assertion that Bannister teaches a subgenus in which B is a fused aromatic or heteroaromatic ring, it is hard to contemplate an answer to such questions without also considering Applicants' own application, which would of course be improper hindsight reasoning. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) ("courts should not succumb to hindsight claims of obviousness").

Since an incredible amount of picking and choosing must be performed in order to arrive at any particular combination of substituents, the Examiner sought to identify several examples in Bannister where certain substituents common to Applicants' elected compound were actually exemplified. To this end, the Examiner stated that "Bannister teaches several examples wherein R_2 is Me, X is NH, Y is N and R_1 is absent." (Office Action page 4.) Notably, however, a molecule with this particular combination of variables **is not** exemplified in Bannister. So while there are examples in Bannister where X is NH and Y is N, nowhere is that combination seen along with R_2 being methyl and with R_1 being absent. As such, the statement by the Examiner that "Bannister teaches several examples wherein R_2 is Me, X is NH, Y is N, and R_1 is absent" is misleading. In truth, there are several examples where, taken individually, some of these variables are present, but there is not a single example where this combination of variables is taught. And of course there are no examples of any kind where ring B is

(...continued)
heteroaromatic ring" (*i.e.* any and all 5-, 6- and 7-membered single-ring aromatic groups, which may include anywhere from 1 to 4 heteroatoms and which may be substituted at one or more positions and which further may include polycylic ring systems having between two and an undefined upper number of cyclic rings, in which only one of the rings need be aromatic). The number of possible permutations encompassed by these definitions is evidently vast and, as such, the Examiner's assertion that this vast number of possible permutations is "a finite number of possible options" is plainly erroneous.

phenanthroline. Hence, the only accurate statements about the examples taught in Bannister is that they **do not** include any compounds in which B is a phenanthroline ring nor do they contain the combination R_2 is Me, X is NH, Y is N, and R_1 is absent, much less this combination with B as phenanthroline.

In summary, the obviousness rejection is flawed because it does not provide a reasoned identification of a known lead compound. The rejection simply begins, without explanation, with a hypothetical compound—which is actually the result of Examiner's own chosen combination of certain variables from a large general formula that match the elected compound 90.

2. Providing reasons to modify the lead compound

To successfully argue that a new compound is obvious, the Examiner must also show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356 (quotation marks omitted). "In keeping with the flexible nature of obviousness inquiry, the requisite motivation [to modify] can come from any number of sources." *Eisai*, 533 at 1357 (citation omitted). But again, as noted in *Takeda,* it still "remains necessary to identify **some reason** that would have led a chemist **to modify a known compound** in a particular manner to establish *prima facie* obviousness of a new claimed compound. *Takeda,* 492 F.3d at 1356-57 (citation omitted). *See also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a *prima facie* case of obviousness requires "structural similarity between claimed and prior art subject matter . . . [and] reason or motivation to make the claimed compositions" (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*))). To put this inquiry in the context of the present application, the Examiner must show that, at the time of invention, a person having ordinary skill in the art would have had reason to attempt to make the claimed compounds, and specifically elected compound 90, and a reasonable expectation of success in doing so. Neither of these two questions (*i.e.*, whether there was (1) reason to make the claimed compounds and (2) a reasonable expectation of success) were addressed by the Examiner.

2.1 Reasons to make the claimed compounds

The "reasons to make the claimed compounds" element can be described as any rational explanation that describes why the skilled artisan would have modified a lead compound in a particular way in order to get to the claimed compounds. Offering such an explanation is of course impossible without first identifying a lead compound that one would modify, which as noted above, the Examiner has not done. It is like trying to explain how to get to a point on a map without specifying a starting point. The Examiner has just said that it is obvious to go to point "A" because it's possible, without stating from where and why.

Even in the absence of identifying a known lead compound as a starting point for modification, the Examiner attempted to offer the following as the reason for preparing the elected compound: "one would have been motivated to do so because the elected compound is suggested from a finite number of possible combinations." (Office Action page 5.) This is not a sufficient reason. The Examiner's attempt to qualify this statement by identifying a "much smaller" subgenus in which B is a fused aromatic or heteroaromatic ring and alleging that phenanthroline is one of a "finite number of options" identified for B remains insufficient.

The elected compound is not "suggested." Nothing in Bannister can be said to point anywhere in the direction of the claimed compounds. The Federal Circuit has cautioned against a finding of obviousness "where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The particular combination of substituents the Examiner cites is simply within Bannister's disclosed genus. The motivation to make a species or a subgenus within a broad genus cannot simply be based upon the possibility that one could make the compound or on the fact that the species or subgenus is within the genus. The Examiner is required to "identify some reason that **would have led a chemist to modify a known compound in a particular manner** to establish *prima facie* obviousness of a new claimed compound. *Takeda,* 492 F.3d at 1356-57 (citation omitted; emphasis added). See also MPEP at §2144.08 (4) where it states that for "obviousness of species when prior art teaches genus" the key factor to determine is whether "it **would have been**

obvious to one of ordinary skill in the relevant art to make the claimed invention as a whole, *i.e.*, **to select the claimed species or subgenus from the disclosed prior art genus**" (emphasis added). Stating that a chemist **could** select a particular combination of substituents in Bannister is not the same as providing a reason that a chemist **would** have selected the combination.

2.2 Expectation of success in making the claimed compounds

Another error arises when one considers the reason offered by the Examiner for alleging obviousness—that Bannister suggested the claimed compounds from a "finite number of possible combinations." In addition to being flawed because Bannister does not suggest the claimed compounds (as discussed above), this reason is flawed because of its characterization both of Bannister's formula as a "finite number of possible combinations" and of phenanthroline as being one of a "finite number of options" for B. Such phrases imply that there is some manageable number of combinations to deal with and that selecting a given combination or option would be a choice that one could fairly believe would be successful. This is not a fair treatment of the disclosure of Bannister.

These statements by the Examiner seem to be an attempt to align this rejection with a sentence from *KSR*. In *KSR* the Supreme Court stated that when a person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 421. But the circumstances surrounding Bannister involve an overly broad genus of chemical compounds and a very large subgenus (see footnote 1 *supra*) and are therefore very different from the situation in *KSR*. It is therefore wrong to suggest that as in *KSR* the situation here merely involves a selection from a "finite number of identified predictable solutions."

Shortly after *KSR*, the Federal Circuit cautioned that, "[t]o the extent an art is unpredictable, as the chemical arts often are, KSR's focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai*, 533 F.3d 1353, 1359 (quoting *KSR*, 550 U.S. at 421). *See also Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341 (Fed. Cir. 2008) ("We agree that the obviousness of selection of components, when there is no prediction in the prior art as

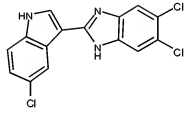
to the results obtainable from a selected component, differs from the issue in *KSR*, where the Court provided guidance that 'a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.'. . . The Court in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology.") The Office Action ignores this distinction and alleged that in arriving at the claimed compounds Applicants have done nothing more than picked from a few known options and got just what they expected. Specifically, the Office Action stated that "when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." (Office Action page 6.)

This statement is quite surprising. It is erroneous to contend that substituents on a molecule are mere "old elements" that one can simply stick on at a whim and with every expectation of success. If this statement were true, then every chemical compound that has or will be made is obvious—a chemist could be said to pick from "old elements," a methyl group here with a heterocycle there, perhaps add a hydroxyl group, stick them all together and obtain "no more than one would expect from such an arrangement." This is not how chemistry is done nor how obviousness is determined. Different molecular substituents are not "old elements" that can be assumed to perform "according to their established functions."[2] (Office Action page 6.) Because these groups can be present, and because a skilled chemist can put them on a molecule, says nothing about an expectation of success in doing so.

Perhaps the error in asserting a reasonable expectation of success can be understood by considering the Examiner's definition of success. It appears that the definition of success used in the rejection is that the compound can be made, without regard to any purpose or utility. This is not what the courts mean by a reasonable expectation of success. *See e.g.*, *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal Inc.,* 231 F.3d 1339, 1345 (Fed. Cir. 2000) (Such a "level of motivation" did

not show a "reasonable expectation of success" because success in this field was a compound with high activity, few side effects, and low toxicity). In the context of Bannister then, a meaningful success would have to take account of the established purpose of the described compounds (*i.e.* as anti-microbial agents). Likewise, in the context of the presently claimed compounds, a meaningful success must take account of the established purpose of the compounds (*i.e.* as anti-cancer agents), a purpose neither taught nor suggested by Bannister. How a skilled worker could have a reasonable expectation of modifying any compound taught by Bannister to successfully produce an anti-cancer agent when such a purpose is not even suggested by the art, is another point the Examiner has failed to address.

Furthermore, when one fairly considers the disclosure of Bannister it is evident that the reference does not give an expectation of meaningful success if they were to prepare the claimed compounds, even when meaningful success is limited to achieving the anti-microbial purpose described in Bannister. For the sake of argument, and to illustrate this point, assume that the skilled artisan had a reason to select the following compound as the lead compound.



This is an actual compound from Bannister (Figure 7) and one that is shown to be relative active against bacteria (MIC < 1 μg/mL). Further, this compound would seem to require the least number of chemical transformations to arrive at the elected species compound 90 as compared to the other exemplified compounds in Bannister. So for a chemist to modify this lead compound and arrive at compound 90, they would have to remove the dichlorophenyl group and substitute therefor the much larger phenanthroline group, add a methyl to the indole ring, and remove the chlorine on the indole ring.

(...continued)

[2] The Examiner is invited to explain the "established function" of a methyl group, of a halogen, of a (continued...)

There is simply nothing from Bannister (or anywhere else) that would suggest making any, much less all of these chemical transformations, with any likelihood of obtaining success (a meaningful success, not "success" as in being able to make the compound with no reason). In fact, when one considers the data of Bannister, substitution of one of the chlorines on the benzimidazole ring with a larger methyl ester, results in the MIC going from <1 to over 25 (see Figure 7). So, one would not think to replace the dichlorophenyl group with a much larger phenanthroline ring or phenanthrene ring structure when the less sterically drastic replacement with a chloro-methylester-phenyl resulted in greatly decreased activity. *In re O'Farrell*, 853 F.2d 894, 903-04, (Fed. Cir. 1988) ("There can be little better evidence negating an expectation of success than actual reports of failure.")

The reason to make this change from halogenated phenyl to a phenanthrolyl or phenanthrenyl structure is even more attenuated when one considers that all of the compounds exemplified in Bannister have as the B ring, a phenyl group with at least one halogen (*i.e.*, comprise a halogenated benzimidazolyl moiety). This moiety would seem then to be essential (at least that is a more reasonable interpretation of Bannister than for one to say that the benzimadazolyl moiety is not important and easily substitutable). The exclusive use of the benzimadazolyl moiety does not suggest that the skilled artisan could, with a reasonable expectation of meaningful success, replace it with a phenanthroline or phenanthrene ring structure. It may be possible to do this but it is certainly not suggested.

For another example, consider that all of the examples of Bannister have either a chlorine or a bromine on the indole ring. So again, this suggests that such a substituent is essential and not readily substitutable or removable. Still further, all of the examples lack a methyl group on the indole ring. And thus there is no suggestion for the addition of a methyl group here, though it may be possible. Taken together, it is just not the case that Bannister or anything else provides a reason to make not only a substantial modification by substituting a halogenated phenyl for a phenanthrolyl/phenanthrenyl, but also two other major modifications (removal of chlorine on indole and adding methyl on indole) to

(...continued)
phenanthroline, and the like.

a lead compound and arrive at the elected species compound 90 with any expectation of success. Even if one were to start from a much narrower group of compounds, there is no expectation of success. *In re Baird* 16 F.3d 380, 383 (Fed. Cir. 1994) (observing that "it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved").

Summary of conclusions

The Office Action rejection regarding obviousness is improper on a number of fronts. It does not begin with a reasoned identification of a lead compound; instead, simply picking various variables that match the elected species. No reasons are given for the selection of the variables other than that they are possible from the formulae of Bannister. Moreover, no reasons are provided for arriving at the elected species. All that is offered is that Bannister provides examples with the selected combination of variables, which is in fact not true. Further still, no reasonable expectation of success is identified. The only thing offered on that point is that the selection is possible from a finite number of possibilities. Applicants have shown how that conclusion is flawed on various grounds (*i.e.*, it is a vast number of possibilities and there is no suggestion to make even one of the needed modifications in order to arrive at the claimed compounds, much less at the elected species).

The Examiner is encouraged to consider the case *Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), discussed above. Like in Bannister, there was nothing in the prior art of *Takeda* to narrow the possibilities within the disclosed genus to a few, predictable alternatives. And rather than identify predictable solutions, the prior art in *Takeda* disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Thus, this case fails to present the type of situation contemplated by the Court in KSR when it stated that an invention may be deemed obvious if it was "obvious to try." *Takeda*, 492 F.3d at 1359. The *Takeda* Court focused on the Supreme Court's requirement in *KSR* that the claimed solution be "predictable" before it can be invalidated on "obvious to try" grounds and, thus, concluded that a *prima facie* case of obviousness had not been established. Accordingly, Applicants respectfully submit that the Office

Action has failed to set forth a *prima facie* case of obviousness with respect to the claims of the present application.

Double Patenting

The Examiner has provisionally rejected Claims 21-22, 24-27 and 39 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 25 and 42 of the copending Application No. 10/525,690 and Claims 1-55 of the copending Application No. 11/915,257. Applicant acknowledges the rejection and will formally respond in the appropriate application once claims are found to be allowable, necessitating the removal of the provisional status of the rejection.

Other Matters

The Examiner is reminded that in order to retain the right to rejoinder for the unelected process claims, the process claims must be amended during prosecution to require all the limitations of the product claims. In this regard, we note that Claim 28, directed to a method of treating cancer, refers directly to the compounds of currently pending product Claim 21. Applicants have further amended dependent method claim 37 to reflect the amendments made to dependent product Claim 26. As such, pharmaceutical composition Claim 27 and method Claims 28 to 39 are in order for rejoinder with the currently pending product Claims 21 to 26.

CONCLUSION

In light of the arguments presented above, the claims are believed to be in condition for allowance. Accordingly, notification of same is earnestly requested.

Enclosed is payment in the amount of $650.00, which includes the $245.00 fee for the Two-Month Extension of Time under 37 C.F.R. § 1.17(a)(2) and the $405.00 fee for the RCE under 37 C.F.R. § 1.17(e) (small entity). This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,
BALLARD SPAHR LLP

/Christopher L. Curfman/

Christopher L. Curfman
Registration No. 52,787

BALLARD SPAHR LLP
Customer No. 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF EFS-WEB SUBMISSIOM UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being filed via EFS-WEB with the United States Patent and Trademark Office, on the date indicated below.

/Christopher L. Curfman/	November 6, 2009
Christopher L. Curfman	Date